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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/829,621	04/10/2001	Moshe Flashner-Barak	1662/52202	7987

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KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER
PULLIAM, AMY E

ART UNIT	PAPER NUMBER
1615	11

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/829,621	FLASHNER-BARAK, MOSHE	
	Examiner	Art Unit	
	Amy E Pulliam	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29, 32-59, 62-71* is/are pending in the application.

4a) Of the above claim(s) *10,11,19,20,23,38,39 and 49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12-18,20-22,24-29,32-37,40-48,50-59 and 62-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9,10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt of Papers

Receipt is acknowledged of the First Supplemental IDS and the Amendment B, both received by the Office March 10, 2003, and the Second Supplemental IDS, received March 28, 2003.

Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection, found below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-7, 12-18, 20-22, 24-29, 32, 33, 40-48, 50-52, 55-59, and 62-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/61141 to Au *et al.*.

Au *et al.* disclose methods for enhancing the delivery of therapeutic agents into the interior of tissues, such as solid tissues or tumors (abstract). The methods involve use of an apoptosis inducing agent, such as paclitaxel, in doses and for periods of time sufficient to cause apoptosis in the tissue to thereby allow for enhanced penetration of the therapeutic agent into the tissue (page 2, lines 29-32). Therefore, Au *et al.* teach, the apoptosis inducing agent is used as a pretreatment before the therapeutic dose of the therapeutic agent is delivered to the tissue, and

this pretreatment allows for enhanced penetration of the therapeutic agent into the tissue as compared to when the pretreatment is not used (page 3, lines 1-3). The reference teaches that the apoptosis inducing agent and the therapeutic agent can be the same drug (page 3, lines 5-6). Au *et al.* also teach that the invention includes nanoparticles and microparticles comprising therapeutic or apoptosis inducing agents, and methods of treating patients using the particles (page 4, lines 5-8). These microparticles refers to particles of about 0.1 microns to about 100 microns (page 11, lines 10-15). Au *et al.* also teach that the apoptosis inducing agent and the therapeutic agent can be administered simultaneously, in a slow release formulation (page 19, lines 1-5). Au *et al.* further explain that the dose of the apoptosis inducing agent can comprise the dose of the therapeutic agent in a slow release formulation (page 22, lines 15-20).

Au *et al.* also teach that the invention pertains to a composition which comprises a microparticle and a pharmaceutically acceptable carrier, which may be acceptable for local, regional, or locoregional administration (page 24, lines 16-20). Also, at page 5 it is again stated that the apoptosis inducing agent and the therapeutic agent can be in the same dosage form (page 25, lines 3-5). Au *et al.* also teach the use of suspensions (page 27, lines 23-27). Additionally, Au *et al.* teach the use of paclitaxel.

Au *et al.* also do not teach the amount of drug release within a specific amount of time, as claimed by Applicant. However, the reference does teach that slow release means the formulation releases the therapeutic agent for anywhere from 6 hours to 5 days after administration (page 14, lines 17-24). It is the position of the examiner that this broad teaching allows for routine manipulation of the formulation, creating different rates of release depending

upon the desired effect. Absent evidence to the contrary, it is the position of the examiner that the broad teachings of Au *et al.* suggest Applicant's broad claims.

Au *et al.* do not specifically teach that the formulation comprises the anti tumor agent in the microspheres, with the apoptosis inducing agent in the suspending solution. However, it is the position of the examiner that the teachings of Au *et al.* suggest such a formulation. First, Au *et al.* teaches the importance of a formulation comprising both an apoptosis inducing agent and a chemotherapeutic agent (which can be the same drug). Second, Au *et al.* teaches that the apotosis agent must have time to cause apoptosis, followed by the release of the therapeutic agent. Third, Au *et al.* teach that the two components can be administered from the same dosage form, but it is important that the apoptosis inducing agent be released first. Therefore, this clearly calls for a dosage form with immediate release of the apoptosis inducing agent, followed by sustained release of the therapeutic agent. Relying upon Au *et al.*'s teaching of suspension formulations and microparticles, one of ordinary skill in the art would clearly have the motivation to create sustained release microspheres comprising the therapeutic agent, to be suspended in a solution comprising the apoptosis inducing agent, so as to allow immediate release of the apoptosis inducing agent and sustained release of the therapeutic. Au *et al.* does not provide specific guidance for this formulation, but it is clearly suggested in the language of the specification. Therefore, this invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8, 9, 36, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Au *et al.* in view of US Patent 6,277,391 to Seo *et al.*.

Au *et al.* do not provide details regarding the use of microspheres, how to make said microspheres, or how to use said microspheres in a suspension. However, the reference does state that all well known formulations can be made through methods which are known in the art. Seo *et al.* are relied upon to teach what is known in the art.

Seo *et al.* teach a composition and method for treating diseases and disorders of the prostate. More specifically, Seo *et al.* teach a microsphere formulation comprising microspheres suspended in a liquid (c 3, l 43-45). The therapeutically effective substance will be combined with a biodegrable polymer to form the microspheres (c 3, l 25-26). The active agent can be an anticancer agent (c 3, l 20), such a paclitaxel (c 9, l 33). The biodegrable polymer is a member selected from the group consisting of polylactic acid, polyglycolic acid, or poly(lactic-co-glycolic) acid (c 3, l 32-36). The microspheres are generally between 1 and 100 microns, and the active agent comprises 10-50% of the total microsphere mass. This reference is relied upon to show that paclitaxel is known in microsphere formulations, and to teach a method of making microspheres and what polymers are generally used for this purpose.

One of ordinary skill in the art would have been motivated to look to the teachings of Seo *et al.* to make microspheres comprising paclitaxel. The motivation lies in the teachings of Au *et al.*, which state the paclitaxel microspheres can be formulated according to known methods in the art. Seo *et al.* teaches one such method. The expected result would be a successful formulation comprising microparticles in suspension, which could be used in the method described by Au *et al.* Therefore, this invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 2, 3, 34, 35, 70. and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Au *et al.* in view of WO 99/13914 to Hegedus *et al.*.

Au *et al.* do not teach the inclusion of plasma proteins, such as human serum albumin, in their formulations. Hegedus *et al.* are relied upon for the teaching that paclitaxel in combination with human serum albumin is known in the art and has been successful used in formulations.

Hegedus *et al.* teach an invention related to water soluble products and pharmaceutical formulations in solid or liquid form (abstract). More specifically, Hegedus *et al.* teach that the composition comprises an active agent with a low aqueous solubility and a substantial binding affinity to plasma proteins. The reference teaches either human serum albumin or immunoglobulin as the plasma protein and paclitaxel as the active agent (p 41, claim 10). Hegedus *et al.* also teach that the formulation can be in solid or liquid form (p 43, claim 21). The reference describes the process of making, which includes dissolving the active in a solvent, combining the solution with a solution of the plasma protein, removing the organic solvent and lyophilizing the solution or its concentrate (p 44-45, claim 25).

It is the position of the examiner that the inclusion of a plasma protein in a known microparticle formulation is not patentable, particularly when the combination including the specific active agent and the plasma protein is known in the art. It is the position of the examiner that one skilled in the art would have been motivated to include human serum albumin in the formulation of Au *et al.*, based on the teachings of Hegedus. The expected result would be a stable and successful formulation for treating cancer. Therefore, this invention s a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E Pulliam whose telephone number is 703-308-4710. The examiner can normally be reached on Mon-Thurs 7:30-5:00, Alternate Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3592 for regular communications and 703-305-3592 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

A. Pulliam
Patent Examiner
May 27, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600